REMARKS

Claims 1, 30 and 39 have been amended to delete the divalent group "-$NR^5C(O)NR^5R^{5'}$-," from the element "M" to further prosecution and overcome the rejection under 35 U.S.C. § 112, second paragraph. Applicants do not concede the merits of the rejection and reserve the right to pursue the cancelled subject matter in a continuation application.

Claims 7 and 8 have been cancelled so that subject matter defined therein can be claimed in a separate application which is free of subject matter which conflicts with the claims in US Patent 6,319,921.

Claims 35–37 have been canceled and claim 38 has been amended to depend on claim 29 to further prosecution and overcome the rejection under 35 U.S.C. § 102. Applicants do not concede the merits of the rejection and reserve the right to pursue the canceled subject matter in a continuation application.

Claim 25 has been amended to depend on claim 33 to provide further differentiation from claim 24.

Claim 32 has been amended to depend on claim 39 and members of the Markush group of claim 32 without antecedent basis in claim 39 have been cancelled. The cancelled subject matter is still encompassed by generic claims 1 and 30.

Enablement

Applicants maintain that all claims satisfy the requirements of 35 U.S.C. § 112, first paragraph, including the method claims.

Claims 15–16 and 18–23 define the conditions to be treated as diseases "mediated by raf kinase." This functional definition is used so as to be consistent with the raf kinase

activity demonstrated in the examples. Claims 26–29 and 38 define methods for treating a solid cancer, melanoma or adenoma.

The specification provides a number of publications which have correlated the inhibition of raf kinase with the inhibition of the growth of a variety of tumor types (Monia et al.), correlated the inhibition of raf expression with blocking cell proliferation (Kolch et al.) or correlated the inhibition of the raf kinase pathway with the reversion of transformed cells to the normal growth phenotype (Daum et al., Fridman et al.).

No evidence has been presented to refute the findings or conclusions made in these publications. In addition, no evidence has been presented that any compounds of this invention, as inhibitors of raf kinase, would not be effective in treating diseases mediated by raf kinase or the cancers identified such as the solid cancers, melanoma or adenoma of claims 26–29. Only unsupported allegations and conclusions regarding the art of cancer treatment are provided as reasons for the rejection such as,

"...no compound has ever been found to treat cancers of all types generally."

"...the record does not identify which diseases are contemplated."

"The specification does not provide a reasonable explanation of the diseases mediated by raf kinase."

"The disclosure does not provide sufficient guidance or direction towards treatment of all 'diseases' mediated by raf kinase."

"There is nothing on the record to enable one skilled in the art to use the compounds in the treatment of all diseases mediated by raf kinase..."

Besides being unsupported, these allegations are not consistent with the record. Applicants do not claim the treatment of all cancer types generally and the publications cited in the

specification and the cancers identified therein provide sufficient direction as to the diseases which are mediated by raf kinase. In addition, the specification provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of this invention and how to administer these compositions. See, e.g., pages 14–16. The specification also provides dosage ranges for the various methods of administration (see page 16) to treat the diseases identified.

Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat any one of the recited cancers with a compound of this invention or a disease found to be mediated by raf kinase. As discussed in Wands, cited by the Examiner, "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Moreover, with respect to pharmaceutical inventions, an applicant is not required to test the claimed compounds in their final use. The Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir. 1995), stated that:

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas.

The courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971) (holding that how an enablement teaching is set forth, either by use of illustrative examples or by broad terminology, is of no

importance.) The disclosure must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. See *In re Marzocchi*, supra. No such evidence or reason for doubting Applicants' disclosure has been provided. Only general statements and conclusions are made.

Additionally, "the [enablement] requirement is satisfied if, given what they [, those of ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the claimed invention without 'undue experimentation'." See *Amgen v Hoechst Marion Roussel*, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Using the claimed compounds would be routine for those of ordinary skill in the art in view of applicant's disclosure.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make and use the compounds recited in the claims. Instead of relying on proper probative evidence, the rejection is improperly based on bare allegations and conclusions. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the use of the claimed compounds without undue experimentation.

Here, the specification provides more than it needs to, e.g., *in vitro* raf kinase assays (and IC_{50} data) and *in vivo* assays. In similar fashion, one of ordinary skill in the art by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating various cancers. This is absolutely routine in the field.

Thus, appellants have provided more than adequate guidance to enable the claimed invention.

For the reasons discussed above, Applicants submit that all pending claims meet the requirements of 35 U.S.C. § 112, first paragraph.

Regan

It is alleged the broad generic disclosure of U.S. Patent No. 6,080,763 (Regan) embraces some of the compounds claimed herein and that it would have been obvious to select "any of the species taught by the reference, including those instantly claimed because the skilled chemist would have had the reasonable expectation that any of the species of the genus would have similar properties and thus, the same use as taught for the genus as a whole." This analysis has been held not to be the law in *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992):

> We decline to extract from *Merck* the rule that the Solicitor appears to suggest – that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it. ... In contrast, though Richter discloses the potentially infinite genus of "substituted ammonium salts" of dicamba, and lists several such salts, the salt claimed here is not specifically disclosed. Nor, as we have explained above, is the claimed salt sufficiently similar in structure to those specifically disclosed in Richter as to render it *prima facie* obvious. (21 U.S.P.Q. 2d at 1943)

No evidence has been presented that any of the compounds claimed herein are sufficiently similar in structure to those specifically disclosed in U.S. Patent No. 6,080,763 so as to render them *prima facie* obvious. Applicants submit that compounds claimed herein can only be found within the genus of US 6,080,763 when this application is used as a guide. Selections must be made for the variables A, B, D, E and G, the variable R_3 and the variable R_5 of Regan to obtain any of the compounds claimed. No evidence of any motivation to make the necessary selections or modify the specific compounds disclosed in US 6,080,763

to arrive at any of the compounds claimed herein has been identified. In the absence of such evidence, applicants submit the rejection under 35 U.S.C. § 103 should be withdrawn.

Method Claims

US 6,080,763 discloses that the compounds described therein are "useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease." There is no hint or suggestion any of the compounds are useful in treating raf mediated diseases or the cancers identified herein such that the method claims 15, 16 18-23, 26-29 and 38 are clearly unobvious in view of this reference.

Claims 33, 34, 39 and 32

Certain claims are directed to compounds wherein "B" is substituted by "M-L^1" and L^1 is a heteroaryl moiety. For example, in claims 33 and 34, L^1 is pyridinyl, quinolinyl or isoquinolinyl. In claim 39, L^1 is pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl. In claim 32, L^1 is pyridinyl, benzothiazolyl, pyrimidinyl, quinolinyl and phthalimidyl.

The broad generic disclosure of Regan (US 6,080,763) does not even encompass such structures in that only phenoxy, naphthyloxy, phenylamino, naphthylamino and similarly bridged phenyl and naphthyl groups are disclosed. There would be no motivation to prepare the compounds of this invention where L^1 is heteroaryl in that Regan (US 6,080,763) does not provide any compounds with a bridged aryl structure to be modified. Therefore, these compounds are truly unobvious over Regan.

U.S. Patent No. 6,319,921

Applicants acknowledge U.S. Patent No. 6,319,921 and respectfully decline to cancel conflicting subject matter. Subject matter which does not conflict with the claims of US 6,319,921 will be presented in a separate application.

In view of the above, favorable reconsideration is courteously requested. If there are any remaining issues which can be expedited by a telephone conference, the examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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